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Pharmacokinetic Interaction between Rifampin and Zidovudine

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A potential pharmacokinetic interaction between rifampin (Rimactan, Rifadin) and zidovudine (AZT, Retrovir) was investigated in the population of human immunodeficiency virus-infected patients at our hospital. The results from four patients who were on long-term (≥6 months) combination therapy with zidovudine and rifampin are presented. In all cases of combined use of zidovudine and rifampin, a lower area under the plasma concentration-time curve (AUC) and, consequently, a higher apparent clearance of zidovudine were found, compared with a reference population of zidovudine users. Patients had a low to normal maximum concentration of zidovudine in plasma. Elimination half-lives were normal in all but one patient. Zidovudine glucuronide concentrations were determined in three patients and three control subjects. The patients all had relatively higher peak plasma concentrations and higher AUCs of zidovudine glucuronide than the control subjects. In one patient, zidovudine and zidovudine glucuronide were also measured 2.5 months after discontinuation of rifampin. The AUC of zidovudine increased by a factor of 2. These data are in agreement with an enzyme-inducing effect of rifampin on the glucuronidation of zidovudine. They indicate that long-term combination therapy of rifampin and zidovudine leads to increased clearance of zidovudine, which may have therapeutic consequences.

Zidovudine (AZT, Retrovir) and rifampin (Rifadin, Rimactan) are both frequently used in human immunodeficiency virus-infected patients. Five years after its introduction, zidovudine is considered to be the cornerstone of antiretroviral drug therapy. Its efficacy in increasing survival in patients with AIDS and in delaying progression to AIDS in patients with AIDS-related complex or asymptomatic seropositive individuals with low $CD4^+$ counts has been well documented (17). Rifampin is a widely used drug in treatment regimens for infection with *Mycobacterium tuberculosis* (7, 12) or *Mycobacterium avium* (8, 13). Because the incidence of mycobacterial infections has increased in the AIDS population during the last years, concomitant administration of zidovudine and rifampin will occur frequently.

A pharmacodynamic drug-drug interaction between zidovudine and antimycobacterial agents (including rifampin) has been investigated in two small studies. Both studies showed no additive toxicity of the combination compared with zidovudine alone (2, 14). Pharmacokinetic investigations, however, have not been reported in the literature as yet. Rifampin is a well-known inducer of hepatic microsomal enzymes (28), and it may influence zidovudine pharmacokinetics, because the latter drug is metabolized extensively in the liver (6).

We report here the results of pharmacokinetic monitoring of zidovudine in four patients who were treated with zidovudine as well as with rifampin for several months and compare the pharmacokinetic data with those from our population of zidovudine users. Zidovudine pharmacokinetics were also determined in one of these four patients after he had stopped taking rifampin.

MATERIALS AND METHODS

Patient population. Since 1988, we have measured zidovudine pharmacokinetics in the population of HIV-infected individuals at our hospital. Patients are eligible when they start treatment with zidovudine or when the responsible physician suspects a change in the pharmacokinetic profile (for example, if toxicity occurs or if a drug interaction is possible, etc.). The study protocol has been approved by the hospital's Drugs and Ethical Committees. The four patients who were on long-term therapy with zidovudine and rifampin were included with the purpose of investigating a potential interaction between the drugs. Patient characteristics are listed in Table 1 (median values plus ranges).

Drug administration. Zidovudine (Retrovir; Wellcome Pharmaceuticals BV, Utrecht, The Netherlands) and rifampin (Rimactan; Ciba-Geigy BV, Arnhem, The Netherlands) were obtained from the hospital pharmacy. Patients fasted overnight and were not allowed to drink or eat until 90 min after drug intake, with the exception of 100 ml of water during drug administration. Since August 1992, patients are no longer requested to ingest a standard dose of 300 mg of zidovudine for pharmacokinetic monitoring, but are allowed to take their usual morning dose. As a result, we have gathered three populations of zidovudine users: population A (300 mg of zidovudine in the morning), population B (200 mg), and population C (100 mg).

Drug analysis. Zidovudine, zidovudine glucuronide, and rifampin levels were measured in plasma obtained from whole-blood samples withdrawn just before and 5, 10, 20, 30, 45, 60, 90, 120, 150, and 180 min after intake of zidovudine and rifampin. Zidovudine levels were measured with a high-performance liquid chromatography (HPLC) assay as previously described (27). Since September 1992, zidovudine is measured by a radioimmunoassay (RIA), the ZDV-Trac (Sorin Biomedica, Amsterdam, The Netherlands) (25). An acceptable correlation between HPLC and RIA values was found by us (correlation coefficient of 0.98 of 61 random samples measured with both HPLC and RIA) and others (25). The detection limits of the assays were 20 and 10 ng/ml for HPLC and RIA, respectively (the actual detection limit of the RIA is lower, but the AIDS Clinical Trials Group recommends a threshold of 10 ng/ml to avoid false-positive

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TABLE 1. Characteristics of patients[a]

Characteristic	300 mg of zidovudine			200 mg of zidovudine		100 mg of zidovudine	
	Population A	Patient 1	Patient 2	Population B	Patient 3	Population C	Patient 4
n	53			4		12	
Wt (kg)	66 (54–86)	85	59	62 (53–90)	60	69 (50–80)	69
Age (yr)	33 (23–61)	37	41	43 (27–45)	33	40 (30–68)	47
Time on zidovudine (mo)	0 (0–32)	9	21	13 (0–24)	16	11 (0–32)	6
With AIDS (*n*)	44			3		11	
With AIDS-related complex (*n*)	4			1			
Asymptomatic (*n*)	5			1			
$CD4^+$ counts (cells/μl)	100 (0–600)	100	70	80 (10–390)	40	53 (10–390)	20
Hemoglobin (g/dl)	12.7 (9.2–17.9)	12.2	11.3	11.3 (9.8–12.2)	10.6	11.6 (8.5–13.5)	7.8
Hematocrit (liter/liter)	0.38 (0.28–0.53)	0.37	0.32	0.35 (0.30–0.39)	0.31	0.34 (0.26–0.40)	0.38
Leukocyte count (10^9/liter)	3.7 (1.6–8.3)	4.4	3.3	3.0 (2.4–8.3)	2.0	2.6 (1.5–8.3)	4.6
Granulocyte count (10^9/liter)	1.8 (1.0–5.5)	2.8	1.7	1.9 (1.3–5.5)	1.3	1.3 (0.6–5.5)	1.4
Platelet count (10^9/liter)	175 (57–358)	206	145	196 (182–227)	83	135 (53–280)	113
Alkaline phosphatase (U/liter)	78 (32–713)	149	86	73 (64–2894)	56	73 (49–199)	126
Gamma-glutamyl-transpeptidase (U/liter)	19 (8–386)	157	45	33 (10–2697)	22	17 (10–239)	112
Aspartate-aminotransferase (U/liter)	18 (7–95)	15	11	16 (8–73)	11	15 (8–49)	21
Alanine-aminotransferase (U/liter)	21 (5–128)	15	11	24 (5–62)	13	16 (5–38)	22
Creatinine (mg/dl)	0.84 (0.60–1.33)	0.86	0.96	0.97 (0.87–1.04)	0.86	0.86 (0.72–1.15)	1.00

[a] All population values are median values, with ranges shown in parentheses.

values [24]). Between-day and within-day variation was always less than 10% for both assays.

Zidovudine glucuronide concentrations were measured with an application of the RIA kit (25). Aliquots of plasma samples were incubated with β-glucuronidase (type X-A; 10,000 U/ml final concentration; Sigma, St. Louis, Mo.) for 60 min at 37°C and were subsequently analyzed by RIA. Incomplete hydrolysis was corrected by using two quality control samples (zidovudine glucuronide concentrations, 324 and 1920 ng/ml; average recovery, 82%). Within-day variation was less than 3.8%. Zidovudine glucuronide levels were measured in patients 2, 3, and 4 (blood samples from patient 1 were not available anymore) and three control subjects who had taken the same dose as the respective patients and who showed median pharmacokinetic parameters for zidovudine (the test for zidovudine glucuronide measurement is not routinely performed at our laboratory).

Rifampin levels were measured by HPLC for only two patients. Briefly, the chromatographic conditions were as follows: column, Lichrosorb (Merck, Darmstadt, Germany) silica (5-μm particle size; 12.5 by 4.0 mm internal diameter); mobile phase, dichloromethane–iso-octane–ethanol–0.12% acetic acid (36.6/45/16.8/1.4, vol/vol); UV detection, 254 nm. Plasma samples (500 μl) were diluted with 50 μl of methanol and 1.00 ml of 0.05 M phosphate buffer (pH 6) and were subsequently extracted with 1.00 ml of extraction fluid (iso-octane–dichloromethane, 3/2, vol/vol). After centrifugation, an aliquot of the upper, organic layer was injected onto the HPLC column. The detection limit was 0.1 mg/liter. Within-day variation was less than 5%.

Pharmacokinetic analysis. Plasma concentration-time (*C-t*) data were analyzed by noncompartmental methods (9). The highest concentration found was defined as C_{max}, with the corresponding sampling time as T_{max}. The terminal, log-linear period was defined by the last N (≥3) datum points (log C, t) by visual inspection of the curves. The absolute value of the slope (β/2.303) was calculated by least-squares analysis. The elimination half-life, $t_{1/2}$, was calculated by the equation 0.693/β. The area under the C versus t curve (AUC) was calculated by using the trapezoidal rule for t_0 to t_{180}, with extrapolation to infinity by the equation C_{180}/β. For comparisons within the whole population, AUC values were normalized to a dose of 100 mg. Apparent clearance, Cl/F, was calculated by dividing dose by AUC, and apparent volume of distribution, V/F, was calculated by dividing Cl by β, where F represents the bioavailability of zidovudine.

Statistical analysis. A Mann-Whitney two-sample test was used to test the difference between normalized AUC values in the four rifampin patients and normalized AUC values in the population of 69 non-rifampin users. A P value of 0.05 or less was considered significant.

RESULTS

Patient 1. Patient 1 is a 37-year-old black homosexual man who received antimycobacterial therapy for *M. tuberculosis* infection for 9 months. The regimen consisted of 600 mg of rifampin once daily, 300 mg of isoniazide once daily, and 1,750 mg of pyrazinamide daily (only for the first 2 months). Zidovudine had been started 1 month before and was continued during antimycobacterial drug therapy, finally at a dose of 500 mg twice daily. The patient tolerated combined treatment well, with no significant bone marrow suppression. Bilirubin and liver enzymes (alkaline phosphatase, aspartate-aminotransferase, and alanine-aminotransferase) remained normal; gamma-glutamyl transpeptidase was increased (four to six times the upper limit of normal) both before and at the end of combined treatment of zidovudine and the tuberculostatics. The patient took no other medication, with the exception of 10 mg of pyridoxine once daily and 15 mg of folic acid daily. Zidovudine was ingested as three 100-mg capsules on the day of pharmacokinetic analysis.

Patient 2. Patient 2 is a 41-year-old white homosexual man who received antimycobacterial therapy for extrapulmonary tuberculosis (lymphadenitis) for 8 months. The regimen was

TABLE 2. Pharmacokinetic parameters of zidovudine[a]

Population or patient given dose of:	AUC (h mg^{-1} $liter^{-1}$)	Normalized AUC (h mg^{-1} $liter^{-1}$)[b]	*Cl/F* (liters h^{-1} kg of body wt^{-1})	$t_{1/2}$ (h)	*V/F* (liters kg of body wt^{-1})	C_{max} (mg/liter)	T_{max} (h)
300 mg							
Population A	2.2 (0.8–10.3)	0.8 (0.3–3.4)	2.1 (0.4–5.6)	0.8 (0.4–3.2)	2.4 (0.6–6.4)	1.8 (0.6–16.5)	0.8 (0.3–2.0)
Patient 1	0.5	0.2	7.3	0.4	4.4	0.4	0.7
Patient 2	0.8	0.3	6.2	0.9	7.8	0.7	0.7
200 mg							
Population B	1.4 (1.3–2.2)	0.7 (0.7–1.1)	1.8 (1.3–2.7)	0.9 (0.8–3.4)	3.7 (1.9–6.3)	1.5 (0.7–3.5)	0.5 (0.3–0.8)
Patient 3	0.9	0.4	3.9	1.0	5.7	0.8	0.8
100 mg							
Population C	0.6 (0.4–2.5)	0.6 (0.4–2.5)	2.4 (0.6–3.9)	0.8 (0.5–2.7)	2.6 (1.3–5.8)	0.5 (0.2–1.7)	1.3 (0.3–2.0)
Patient 4	0.3	0.3	5.5	1.1	8.7	0.4	0.3
Patient 4[c]	0.5	0.5	3.3	0.5	2.5	0.4	0.8

[a] All population values are median values, with ranges in parentheses. For explanation and equations of parameters, see Materials and Methods.
[b] AUC was normalized to a dose of 100 mg.
[c] Data given for period after patient 4 had stopped taking rifampin.

the same as that for patient 1, with the addition of ciprofloxacin (500 mg twice daily) after 4 months. Zidovudine was started 11 months prior to the tuberculostatic regimen and was continued, subsequently, at a dose of 250 mg twice daily. The patient tolerated treatment well, with no signs of bone marrow suppression or hepatic toxicity. He took three 100-mg capsules of zidovudine on the day of pharmacokinetic analysis. Concomitant medication was pyridoxine (20 mg once daily), co-trimoxazole (960 mg once daily), vitamin B complex, vitamin C, folic acid (10 mg once daily), acyclovir (200 mg twice daily), and fluconazole (100 mg daily).

Patient 3. The third patient is a 33-year-old white homosexual man. He started with antimycobacterial therapy 11 months before the pharmacokinetic analysis. Therapy for disseminated *M. avium* infection was started with 750 mg of ciprofloxacin twice daily, 600 mg of rifampin once daily, 1 g of clarithromycin twice daily, and 1,000 mg of ethambutol once daily. Ciprofloxacin and ethambutol treatments were stopped after 2 months. Zidovudine therapy had been initiated in a dose of 200 mg three times daily 4 months prior to antimycobacterial therapy and was continued subsequently. The patient tolerated combination therapy well. On the day of pharmacokinetic analysis, the patient ingested, besides the just-mentioned drugs, co-trimoxazole (480 mg once daily), folic acid (5 mg once daily), and ketoconazole (200 mg every other day).

Patient 4. The fourth patient is a 47-year-old white homosexual man who received antimycobacterial therapy for miliary tuberculosis for 8 months. Therapy was started with 600 mg of rifampin once daily, 275 mg of isoniazide once daily, and 1,750 mg of pyrazinamide once daily. Two months thereafter, pyrazinamide was stopped and zidovudine therapy was started. The patient tolerated combination therapy well. Isoniazide therapy was stopped 1 month before pharmacokinetic analysis. On that day, the patient ingested, besides rifampin (600 mg) and zidovudine (100 mg), co-trimoxazole (480 mg once daily) and folic acid (5 mg once daily). Ganciclovir (7 mg/kg) was injected the day before through a Port-a-cath system. Two and a half months after he had stopped taking rifampin, zidovudine pharmacokinetics were monitored again. Comedication was still co-trimoxazole, folic acid, and ganciclovir. No change in other patient characteristics occurred between the 2 days of pharmacokinetic monitoring.

Pharmacokinetic analysis: zidovudine. Patients 1 and 2 can be compared with population A, patient 3 can be compared with population B, and patient 4 can be compared with population C. Patient 4's data can also be compared with the data obtained after he had stopped taking rifampin. The pharmacokinetic parameters of zidovudine for the reference populations (median values plus ranges) and the four patients are summarized in Table 2. As can be seen in Table 2, the four patients had lower AUC values and higher *Cl/F* values than any individual from the corresponding populations. After normalization of the AUC, three of the four patients had lower AUC values than any other patient from the population (Fig. 1). Statistical analysis revealed that the four rifampin patients (as a group) had significantly lower normalized AUCs than the population of non-rifampin users ($P = 0.0019$, Mann-Whitney two-sample test). C_{max} values of zidovudine were very low in patient 1 and were low to normal in patients 2, 3, and 4. Apparent *V/F*s were high in all

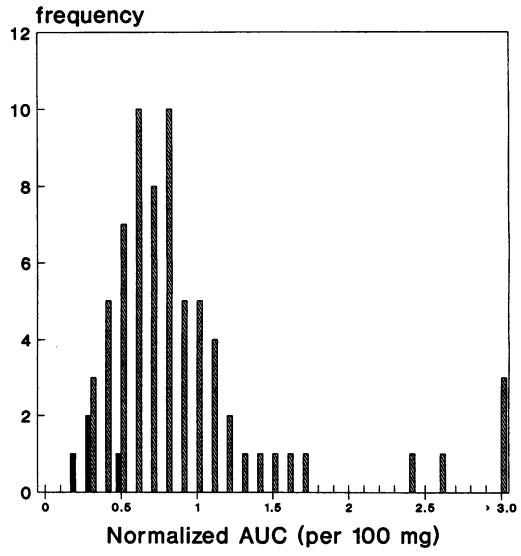

FIG. 1. Frequency histogram of normalized AUC values of zidovudine. Solid bars, rifampin-treated patients ($n = 4$); hatched bars, population ($n = 69$).

TABLE 3. Comparison of C_{max} ratio and AUC ratio of zidovudine glucuronide versus zidovudine for patients and control subjects[a]

Dose of zidovudine	C_{max} ratio[b]	AUC ratio
100 mg		
Patient 4	12.6	21.8
Control subject	4.0	4.4
Patient 4[c]	11.3	13.8
200 mg		
Patient 3	5.4	11.4
Control subject	4.8	8.2
300 mg		
Patient 2	9.8	10.9
Control subject	3.7	6.6

[a] Control subjects were selected from the populations on the basis of a median pharmacokinetic profile and median parameters for that population.
[b] Ratio of peak concentrations of zidovudine glucuronide versus zidovudine.
[c] Data given for period after patient 4 had stopped taking rifampin.

cases. Plasma $t_{1/2}$s of the patients were normal for all patients except for patient 1.

Pharmacokinetic analysis: zidovudine glucuronide. C_{max} ratios and AUC ratios of zidovudine glucuronide versus zidovudine are presented in Table 3. All patients taking rifampin had a higher C_{max} ratio and a higher AUC ratio than the corresponding control patient, who had ingested the same dose of zidovudine. The ratio of C_{max} values remained equal after patient 4 discontinued rifampin, but the ratio of AUC values decreased from 21.8 to 13.8. The plasma *C-t* curves of zidovudine and zidovudine glucuronide are shown for patient 4 in Fig. 2.

Pharmacokinetic analysis: rifampin. Rifampin was measured in only two patients, patients 1 and 2. Maximum levels of rifampin after ingestion of a 600-mg capsule were 7.3 and 10.4 mg/liter for patients 1 and 2, respectively. Plasma $t_{1/2}$s were 2.0 and 1.6 h for patients 1 and 2, respectively.

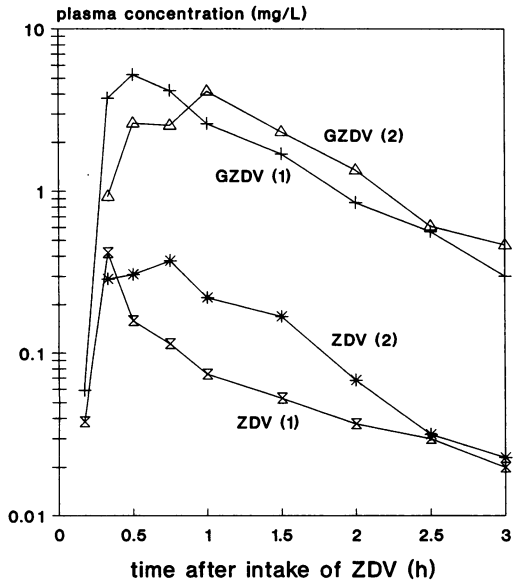

FIG. 2. Zidovudine (ZDV) and zidovudine glucuronide (GZDV) plasma concentrations in patient 4 after a dose of 100 mg of zidovudine during (1) and after (2) rifampin use.

DISCUSSION

All four patients presented here had a lower AUC, and, consequently, a higher *Cl/F* of zidovudine, than non-rifampin users in the population. After normalization of AUC values to a dose of 100 mg, the rifampin patients had statistically lower AUC values than the normal population of zidovudine users. Pharmacokinetic parameters from this population closely resemble previously reported values: *Cl/F* = 2.1 liters/h/kg of body weight (this study and reference 6) and *V/F* = 2.4 liters/kg of body weight (this study; 2.2 liters/kg of body weight in reference 6). Because populations B and C are still small (because of a change in study design), the reliability of the observed effect in patients 3 and 4 is less strong, but after normalization of AUC values, a similar pattern can be seen. In addition, the crossover study of patient 4 clearly showed that the zidovudine AUC while he was taking rifampin was approximately 50% lower than the zidovudine AUC 2.5 months after discontinuation of rifampin.

The observed high levels of zidovudine glucuronide in plasma in the rifampin users, in combination with the low levels of the parent compound in plasma, suggest that metabolism of zidovudine to its major glucuronide metabolite was increased. C_{max} and AUC ratios (zidovudine glucuronide versus zidovudine) reported in the literature are generally not higher than 10 (5, 15, 18, 19, 22, 26), which is also the case for our control subjects. However, in the three patients on rifampin therapy, ratios of 10 and higher were found (Table 3).

For a number of reasons, it is likely that rifampin administration caused this pharmacokinetic interaction. First, only rifampin was present in all patients, and none of the other drugs are known to lower zidovudine levels (16). Furthermore, differences between patient and population characteristics were minimal (Table 1). The possible presence of liver dysfunction in patients 1, 2, and 4 (measured as higher gamma-glutamyl-transpeptidase levels) would result in higher levels of zidovudine (5) instead of the observed lower levels. Finally, a pharmacokinetic interaction between rifampin and zidovudine is plausible, because this has been demonstrated in a small study for rifabutin, a compound structurally related to rifampin. Rifabutin diminished the AUC of zidovudine by 32% and increased *Cl/F* of zidovudine by 43% in eight patients who received 100 mg of zidovudine every 4 h and 300 mg of rifabutin once daily (20). No influence of rifabutin administration on the $t_{1/2}$ of zidovudine could be detected. Likewise, we could not demonstrate this for rifampin.

Rifampin is a well-known inducer of drug metabolism (1, 28). It produces proliferation of smooth endoplasmic reticulum and increases the cytochrome P450 content of the liver. Rifampin's ability to induce drug metabolism, including its own, is shown in patients 1 and 2, where $t_{1/2}$s of rifampin were two-thirds as long as usually seen after single-dose administration (3.3 h [1]), but were in agreement with values reported after repeated administration (2.2 h [1]).

It is plausible that the observed interaction between zidovudine and rifampin is based on induction of liver enzymes. Although induction of liver enzymes by rifampin generally results in a decreased $t_{1/2}$ for a number of drugs (17), this is not the case for drugs with a high hepatic extraction ratio, such as metoprolol (3) and propranolol (11).

We did not find an abnormal $t_{1/2}$ in plasma from patients 2, 3, and 4. Only patient 1 had a relatively low $t_{1/2}$ of zidovudine (0.41 h). This suggests that zidovudine has a high extraction ratio in the liver, which is in agreement with its high presystemic metabolism and short $t_{1/2}$ (6, 15). Furthermore, although rifampin usually induces liver enzymes involved in phase 1 metabolism, such as oxidation and dealkylation (1, 17), it has been demonstrated that it can also increase the glucuronidation of certain drugs, e.g., paracetamol (21). To our knowledge, induction of the glucuronidation of zidovudine by rifampin has not been demonstrated before, but induction by phenobarbital has been reported (10). Therefore, the interaction between rifampin (or rifabutin) and zidovudine is likely to be caused by induction of glucuronidation enzymes in the liver.

Whether the conversion to the cytotoxic 3′-aminocatabolite of zidovudine (23) is enhanced in these patients has not yet been investigated, but an increased (cyto)toxicity of the combination of zidovudine and rifampin was not measured. Lower levels of zidovudine could also be the explanation of the absence of additive toxicity by the combination of zidovudine and rifampin (and other tuberculostatics), as was reported in two pharmacodynamic interaction studies (2, 14).

Theoretically, it would be more reliable to investigate this pharmacokinetic interaction between zidovudine and rifampin in an intrapatient, crossover study. In practice, this is difficult to do, and we succeeded in performing this design only for patient 4. If a patient who uses zidovudine needs antimycobacterial therapy, this should be started as soon as possible. Hence, a pharmacokinetic study before and during combined treatment is not feasible. When patients are included at the end of combined treatment (as was the case for our four patients), one should wait for a long time before induction of liver enzymes has been reversed. During that period, changes in disease stage and/or comedication are likely to occur. The administration of rifampin for a number of months to patients without any indication for its use is not ethical. The only practical way to study this interaction is a crossover design in which patients use rifampin as prophylaxis against mycobacterial infection. Prophylaxis, however, is still under investigation for *M. avium* (8), and isoniazide is the preferred drug for tuberculosis prevention (12). Until that time, reference data must be selected from population studies.

In conclusion, the four patients presented here clearly had a lower AUC and a higher *Cl/F* of zidovudine than patients from the population that did not use rifampin. In addition, the AUC of zidovudine rose nearly twofold after rifampin was discontinued for 2.5 months in patient 4. This effect probably reflects an interaction based on enzyme induction, because metabolism of the glucuronide metabolite of zidovudine was increased in these patients. In view of the diminished sensitivity of the human immunodeficiency virus to zidovudine over time (4), this interaction may have clinical implications in terms of optimal antiretroviral therapy with zidovudine.

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